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Original Research Paper

Preparation and evaluation of sustained-release azithromycin tablets in vitro and in vivo

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ABSTRACT

The objective of this study was to prepare azithromycin (AZI) sustained-release products in order to allow for a high dose to be administered, reduce gastrointestinal side-effects and increase the compliance of patients. AZI sustained-release tablets with different release performance (F-I: $T_{100\%} = 3$ h and F-II: $T_{100\%} = 8$ h in pH 6.0 phosphate buffer) were successfully prepared by wet granulation. The in vitro release rate and drug release mechanism were studied. The release rate of F-I was affected by dissolution media with different pH, but not for F-II. Hixson–Crowell model was the best regression fitting model for F-I and F-II. Additionally, F-I and F-II both belonged to non-Fick diffusion. Oral pharmacokinetics of the two tablets and one AZI dispersible tablet as reference were studied in six healthy beagle dogs after oral administration. Compared with the reference, the C_{max} of F-I and F-II were decreased, and the T_{max} were prolonged, in that case which meet the requirement of sustained-release tablets. The relative bioavailability of F-I and F-II were 79.12% and 64.09%. *T*-test of AUC_{0-144}, and $AUC_{0-\infty}$ for F-I and F-II indicated there was no significant difference between F-I and F-II. These mean that the extended release rate did not induce different pharmacokinetics in vivo.

1. Introduction

Azithromycin (AZI) expands spectrum of antibiotic activity and improves tissue pharmacokinetic characteristics relative to erythromycin [1]. It is absorbed rapidly and has a two-compartment model with peroral administration, while its treatment often has adverse effect on the gastrointestinal tract [2]. Therefore, new drug delivery technology should be

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developed to limit gastrointestinal side-effects of AZI, allow for a high dose to be administered and a full course of antibiotics to be given in a single dose. Azithromycin has an extremely long half-life [3]. This makes it well suited to a single-dose administration. FDA had approved one AZI extended release (Zmax®, Pfizer Inc), that was a novel sing-dose administration formulation. It is currently approved for the treatment of community acquired pneumonia and acute bacterial sinusitis. Recent studies have shown that sustained-release AZI tablets achieve high drug exposure on the first day of therapy at infection sites compared with AZI immediate-release tablets [4,5].

The formulations of sustained-release drug delivery systems wish to achieve desired release rates, decrease the number of daily administrations, improve compliance and minimize side-effects. A hydrophilic matrix is one of sustained-release formulations. It is a homogeneous dispersion of drug molecules within a skeleton in which one or several of the excipients, such as xanthan gum, cellulose derivatives, alginate sodium or carbopol [6].

HPMC is the most widely used as a drug release retardant excipient in hydrophilic matrices. It is soluble in water, non-ionic, stable at a pH between 3.0 and 11.0 and resists enzyme attack [7]. Xanthan gum is a high molecular weight extracellular heteropolysaccharide, produced by fermentation with the gram-negative bacterium *Xanthamonas campestris*. It is widely used in the food industry and in pharmacy practice [8]. Some authors have reported that xanthan gum affords zero-order or at least time-independent release kinetics [9,10]. In this study, HPMC and xanthan gum were used as hydrophilic matrix to prepare sustained-release formulations.

In this study, AZI sustained-release tablets with different release rates ($T_{100\%} = 3$ h and $T_{100\%} = 8$ h in pH 6.0 phosphate buffer) were prepared. The release performances of them were studied in dissolution media with different pH values. Drug release mechanism and the pharmacokinetics of them were studied in detail. Beside, a fast, selective and highly sensitive UPLC-MS-MS for determination of AZI plasma concentration of beagle dogs was developed.

2. Materials and methods

2.1. Materials

AZI was purchased from Shandong Zhongya Pharmaceutical Co., Ltd. (Shandong, China). Hydroxypropyl methyl cellulose (HPMC K100LV) was purchased from Colocrcon Co., Ltd. (Shanghai, China). Lactin (Granulac-200, batch no. 0321) was purchased from Meggle Co., Ltd. (Germany). Microcrystalline cellulose (MCC, batch no. 20071102) was purchased from Yingkou Aoda Pharmaceutical Co., Ltd. (Yingkou, China). Magnesium stearate was purchased from Tianjing Bodi Chemical Factory Co., Ltd. (Tianjing, China). AZI and roxithromycin (ROX) standards were purchased from the National for Control of Pharmaceutical and Biological Products (China). AZI dispersible tablet™ (250 mg, batch no. 091019) was purchased from Jiangsu Huanghe Pharmaceutical Co. Ltd. (Jiangsu, China). All other reagents were either of analytical or chromatographic grade. Double distilled water was used throughout the study.

2.2. Preparation of sustained-release tablets

Formulations I and II were prepared by wet granulation technique (Table 1). All the powders were passed through 100 mesh. Required quantities of drug and excipients were mixed thoroughly, and a sufficient volume of wetting agent (80% or 90% Ethanol) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 20 mesh. The granules were dried at 60 °C for 2 h. Then, the granules were retained on 20 mesh. Magnesium stearate was finally added as glidant and lubricant. Finally, the tablets were compressed. Tablet hardness was controlled between 8.0 and 10.0 N, and the tablet weight was 1.0 g. Each tablet contained 500 mg of AZI and other pharmaceutical ingredients as listed in Table 1.

2.3. In vitro release tests

The in vitro release studies were carried out using RCZ-6B dissolution apparatus (paddle method). The 900 mL dissolution medium was kept at 37 °C and the rotating speed was 100 rpm. The dissolution media used were 0.1 mM HCL, acetate buffer with pH 4.5, and phosphate buffers with pH 6.0, 6.8 and 7.0. F-I and F-II were used in all dissolution studies. Samples were withdrawn from the dissolution media at 0.5, 1, 1.5, 2 and 3 h for F-I, and at 1, 2, 4, 6 and 8 h for F-II. Samples were passed through a 0.45 μm millipore filter and added sulfuric acid solution, then assayed AZI by the UV method.

2.4. Drug release mechanism

Drug release data were analyzed by various mathematical models. Six kinetic models including zero order, first order [11], Higuchi [12], Ritger–Peppas [13], Hixson–Crowell [14] and Baker–Lonsdale release equations were applied to process the in vitro release data. The equations are showed in Table 2.

where Q_t is the drug released fraction at time t, k_0 is the zero order release rate constant, k_1 is the first order release rate constant and k_H is the Higuchi's release rate constant, t is the release time, n is the parameter that depends on the release mechanism and the shape of the matrix tested. The optimum values for the parameters present in each equation were determined by linear or non-linear least-squares fitting

Table 1 – Compositions of 500 mg AZI sustained-release tablets.

Ingredients (per tablet)	F-I	F-II
AZI (mg)	500	500
HPMC K100LV (mg)	80	90
Xanthan gum (mg)	–	20
Lactin (200 screen) (mg)	260	220
MCC (mg)	150	160
Magnesium stearate (mg)	10	10
Ethanol (80%)	qs	–
Ethanol (90%)	–	qs

*qs indicates quantity sufficient.

Table 2 – Models simulated for the release profiles of AZI sustained-release tablets.

Batch No.	Model	Equation	r
F-I	Zero-order model	$Q_t = 31.81t + 9.887$	0.9762
	First-order model	$\ln(96.43 - Q_t) = -0.942t + 4.57$	0.9706
	Higuchi diffusion model	$Q_t = 57.36t^{1/2} - 5.801$	0.9889
	Riteger-peppas model	$\ln Q_t = 0.7301\ln t + 3.829$	0.9940
	Hixson–Crowell model	$(1 - Q_t)^{1/3} = 1 - 0.220t$	0.9960
	Baker–Lonsdale model	$3/2[1 - (1 - Q_t)^{2/3}] - Q_t = 0.124t - 0.047$	0.9623
F-II	Zero-order model	$Q_t = 11.71t + 13.7$	0.9649
	First-order model	$\ln(97.64 - Q_t) = -0.631t + 4.58$	0.6140
	Higuchi diffusion model	$Q_t = 36.02t^{1/2} - 3.497$	0.9955
	Riteger-peppas model	$\ln Q_t = 0.6201\ln t + 3.346$	0.9955
	Hixson–Crowell model	$(1 - Q_t)^{1/3} = 1 - 0.085t$	0.9975
	Baker–Lonsdale model	$3/2[1 - (1 - Q_t)^{2/3}] - Q_t = 0.05t - 0.035$	0.9823

methods. Regression analysis was performed and best fits were calculated on the basis of correlation factors as *r*.

2.5. *In vivo pharmacokinetic study*

The pharmacokinetics was studied in accordance with the Guide for the Care and Use of Laboratory Animals. Six male beagle dogs weighing 10–14 kg were used and divided into 3 groups randomly, and the study was carried out in a crossover experimental design with a washout period of one week. The dogs were fasted for about 12 h prior to experiments, and were given water freely. The preparations (F-I, F-II and AZI dispersible tablet™) were administered orally at a single dose of 500 mg. Five milliliter of blood samples were taken into a heparinized blood collection tube via a detaining needle at pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0, 12.0, 24.0, 48.0, 72.0, 96.0, 120.0 and 144.0 h post-dose. Four hours after dosing, dogs were provided with a standard lunch. The plasma fraction was obtained by centrifuging the samples at 3500 rpm for 10 min, and was stored at −20 °C until analysis.

After precipitation protein by acetonitrile, the AZI concentrations in plasma were determined by liquid chromatography-dual mass spectrometry (LC-MS/MS) method. Roxithromycin (ROX) was used as internal standard. The chromatographic separations were acquired on the ACQUITY UPLC™ system (Waters Corp, Milford, Massachusetts) and BEH C18 column (50 mm × 2.1 mm, 1.7 μm; Waters Corp.) with a mobile phase composed of acetonitrile and ammonia acetate (0–1 min: 50%–90% acetonitrile, 90% acetonirile sustained 0.5 min, 1.5–2.0 min: 90%–50% acetonitrile). The compounds were analyzed by multiple reaction monitoring (MRM) of the transitions of *m*/z 749 → 591 for AZI, and *m*/z 838 → 158 for ROX.

The maximum plasma concentration of AZI (C_{max}) and the time to reach C_{max} (T_{max}) were read directly from the plasma concentration versus time data. The area under curve (AUC) was calculated using the linear trapezoidal rule up to the last data points in plasma concentration-time curve. The elimination rate constant (*k*) was the slope of the terminal four points in plasma concentration-time curve, and the half-life of the preparation ($t_{1/2}$) was calculated by 0.693/*k*. All values were expressed as their mean ± SD. (standard deviation). The relative bioavailability values (*F*) were calculated using following formula with AZI dispersible tablet as a reference:

$$F = \frac{AUC_{test}}{AUC_{reference}} \times 100\% \quad (1)$$

2.6. *In vivo analysis method validation*

2.6.1. *Selectivity*

Selectivity was studied by comparing chromatograms of blank plasma obtained from subjects with those of corresponding standard plasma samples spiked with AZI, I.S., and plasma sample after oral doses of AZI tablets.

2.6.2. *Linearity and lower limit of quantification (LLOQ)*

Calibration curves were prepared by making serial dilution of the working stock and assaying standard plasma samples at six concentrations of AZI ranging 25–5000 ng/ml. The calibration curves were constructed by weighted (1/*x*) least square linear regression. The validation of LLOQ was conducted in at least six different batches of blank plasma. It was validated using an LLOQ sample for which an acceptable accuracy (RE) within ±20% and a precision (R.S.D.) below 20% were obtained.

2.6.3. *Precision and accuracy*

For determining the intra-day accuracy and precision, a replicate analysis of QC plasma samples of AZI was performed on the same day, the run consisted of a calibration curve and six replicates of each low, mid, and high concentration quality control samples. The inter-day accuracy and precision were assessed by analysis of three batches on different days. The precision was expressed as the relative standard deviation (R.S.D.) and the accuracy as the relative deviation (RD).

2.6.4. *Extraction recovery and matrix effect*

The extraction recovery of AZI was calculated by comparing the peak areas of blank plasma samples which adding AZI and ROX before extraction to adding AZI and ROX after extraction. This procedure was repeated for six replicates at three concentrations of 50, 1000, 4000 ng/ml. In order to evaluate the matrix effect on the ionization of analyte, AZI at three concentration levels were added to the extract of 50 μL of blank plasma, the corresponding peak areas (A) were compared with those of the AZI standard solutions evaporated directly and make the water instead plasma. The ration (A/B × 100) % was used to evaluate the matrix effect. The matrix effect of internal standard was also evaluated using the same method.

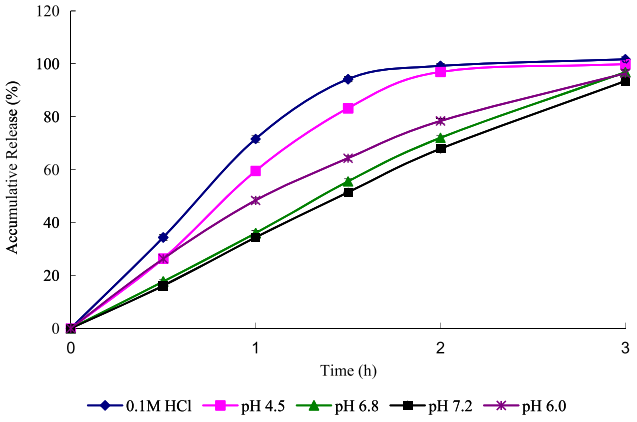

Fig. 1 – Dissolution of AZI sustained-release tablet F-I in 0.1 mM HCL, acetate buffer with pH 4.5, and phosphate buffers with pH 6.0, 6.8 and 7.2. (Data are mean ± SD., $n = 6$).

2.6.5. *Stability*

The effect of freeze and thaw cycles on the AZI stability in plasma was determined by analyzing AZI concentration (low, mid and high concentration) in plasma sample which meeting four freeze-thaw cycles. After completion of every cycle, the samples were analyzed and the experimental concentrations were compared with the nominal values. The accuracy values of three concentrations in four freeze-thaw cycles were calculated.

In order to estimate the stability of AZI in the prepared sample, three QC samples at low, mid and high concentration were kept in sample room about 6 h. Then, the samples were analyzed and the concentrations obtained were compared with the nominal values.

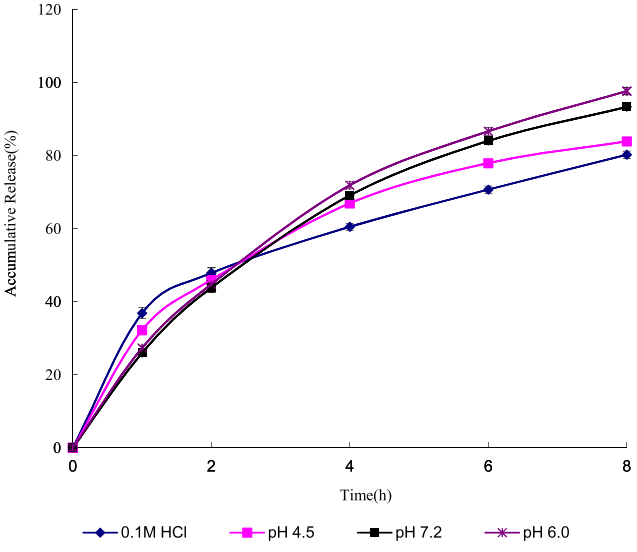

Fig. 2 – Dissolution of AZI sustained-release tablet F-II in 0.1 mM HCL, acetate buffer with pH 4.5, and phosphate buffers with pH 6.0 and 7.2. (Data are mean ± SD., $n = 6$).

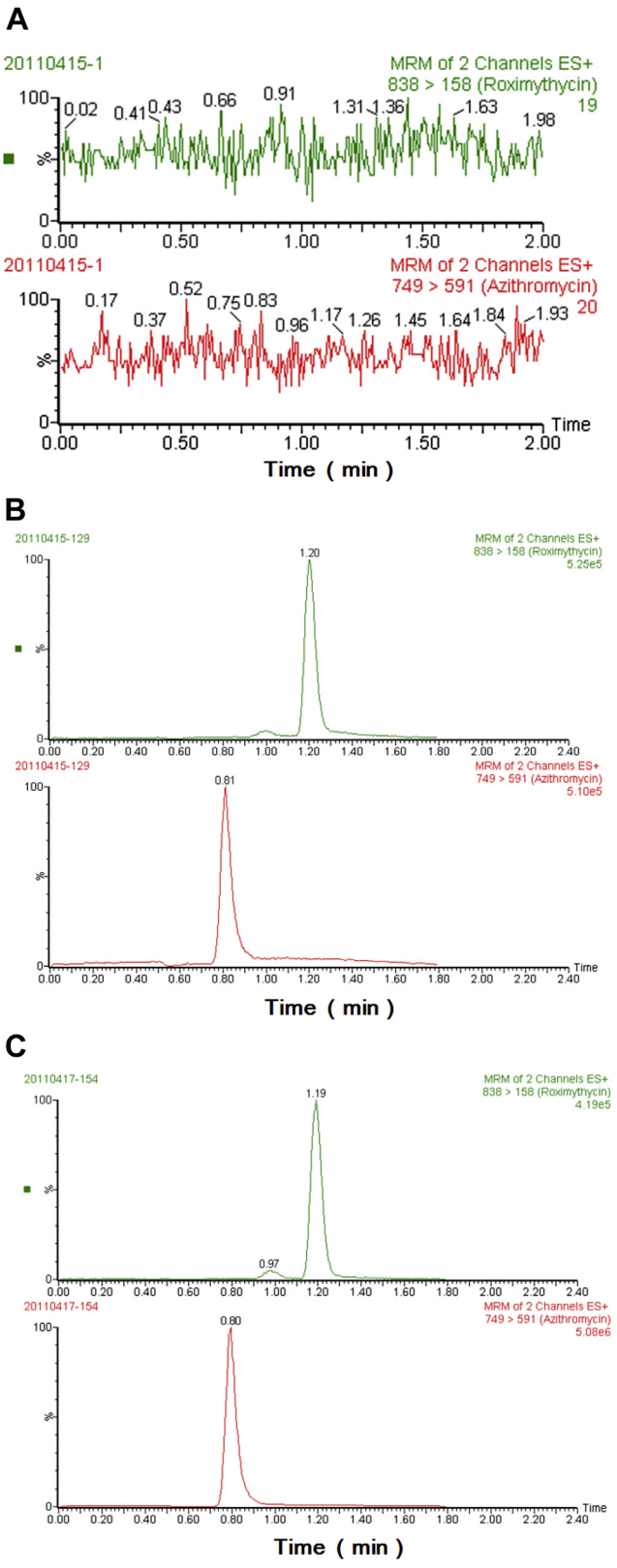

Fig. 3 – Representative MRM chromatograms for roxithromycin and azithromycin from (A) blank plasma sample; (B) blank plasma with internal standard of roxithromycin and azithromycin; (C) plasma sample with internal standard Roxithromycin and Azithromycin.

Table 3 – The absolute recovery of AZI in dog plasma.

	Azithromycin			Roximythromycin
	50 (ng/ml)	1000 (ng/ml)	4000 (ng/ml)	200 (ng/ml)
Recovery/%	85.15	84.91	95.40	88.65
	76.68	86.93	95.23	92.40
	81.78	74.56	99.42	98.64
	81.13	78.77	75.76	86.49
	90.61	78.05	79.32	103.16
	95.22	81.97	87.50	91.58
Mean ± SD/%	85.10 ± 6.79	80.86 ± 4.61	88.77 ± 9.59	93.49 ± 6.28
RSD/%	7.98	5.70	10.80	6.72

3. Results and discussion

3.1. Dissolution test

The in vitro dissolution profiles of F-I and F-II were shown in Figs. 1 and 2. F-I released 100% within 3 h, and F-II released 100% within 8 h. The release behavior of F-I was affected by pH of dissolution medium. However, the release behavior of F-II was not. The skeleton material of F-I is HPMC, which is a non-ionic polymer. The property of HPMC is not dependent on the pH of dissolution media. The solubility of AZI decreased with increasing pH of media, inducing the release rate of F-I became slow with increasing pH of media. For F-II, the skeleton material is Xanthan gum, which is an anion polymer. The property of Xanthan gum is dependent on the pH of dissolution media. In acidic dissolution medium, the ions make the glass transition temperature of Xanthan gum become higher [15,16], hydrating rate becomes slowly. Then, in the early stages of release (about 0–3 h), it is difficult to form gel layer, resulting in the quick release of drug. In the middle period, the ions decreases the degree of swelling, increases the strength of gel layer. As a result, in the final stage of release, the drug release slowly.

3.2. Drug release mechanism studies

In order to explore the mechanism of drug release, drug release data were analyzed by six mathematical models. As shown in Table 2, through various types of regression model parameters and comparing, Hixson–Crowell model was the best regression fitting degree for F-I and F-II. Additionally, the data of F-I and F-II showed values of "*n*" in Riteger-peppas model between 0.45 and 0.89, which could be attributed to non-Fick Diffusion (Table 2).

Table 4 – Stability of AZI in dog plasma under indicated conditions (mean ± SD, *n* = 3).

	Added (ng/ml)	Found (ng/ml)	Accuracy/%	RSD/%
Pretreatment for 6 h	50	51.2 ± 1.67	102.4	3.26
	1000	937.3 ± 42.52	93.73	4.53
	4000	3806.1 ± 59.35	95.15	1.55
Freeze-thaw stability (36 h, *n* = 3)	50	52.03 ± 5.40	104.06	10.38
	1000	931.3 ± 18.02	93.13	1.93
	4000	3632.2 ± 118.1	90.81	3.25

3.3. HPLC method validation for determination plasma samples

3.3.1. Selectivity

No interference from endogenous substance was observed at the retention time of AZI and ROX (Fig. 3).

3.3.2. Linearity and LLOQ

The standard calibration curves for AZI were linear over the concentration range of 25.0–5000.0 ng/ml ($r^2 > 0.99$). The lower limit of quantification for AZI was 25.0 ng/ml with RE within ±20% and R.S.D. lower than 20%.

3.3.3. Precision and accuracy

The intra-day precision for low, middle and high QC levels of AZI were 5.68%, 5.53% and 2.04%, and that of inter-day analysis were 5.39%, 7.49% and 10.05%. The accuracy of low, middle and high QC levels of AZI were 99.48%, 103.10% and 97.59%.

3.3.4. Extraction recovery and matrix effect

The extraction recoveries of AZI from dog plasma were 85.10 ± 6.79%, 80.86 ± 4.61% and 88.77 ± 9.59% at concentration levels of 50, 1000 and 4000 ng/ml (Table 3).

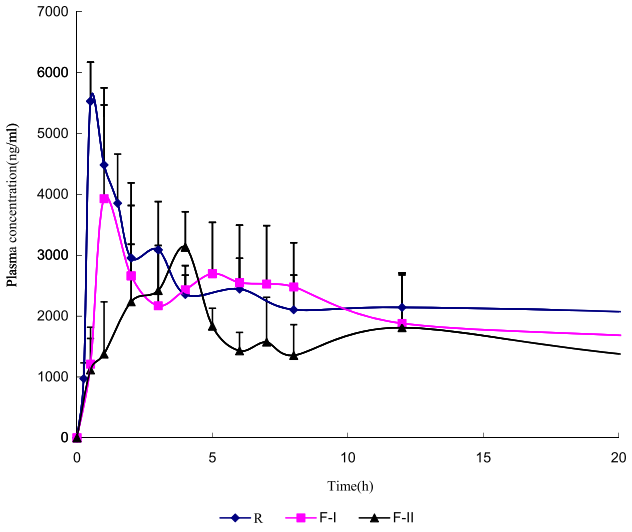

Fig. 4 – Average azithromycin plasma concentration-time curves following oral administration of the three formulations in beagle dogs (Mean ± SD).

Table 5 – Pharmacokinetic parameters of reference, F-I and F-IIAZI tablets (mean ± SD, $n = 6$).

	k_e (h^{-1})	$t_{1/2}$ (h)	C_{max} (ng/ml)	T_{max} (ng/ml)	AUC_{0-144} (ng h/ml)	$AUC_{0-\infty}$ (ng h/ml)
reference	0.01 ± 0.00	73.71 ± 46.60	5558.55 ± 612.14	0.58 ± 0.20	1,84,797.81 ± 32,551.65	2,52,633.25 ± 88,903.26
F-I	0.02 ± 0.01	58.78 ± 22.79	4115.13 ± 1654.54	3.17 ± 3.37	1,44,692.82 ± 48,231.96	1,74,459.75 ± 44,979.14
F-II	0.02 ± 0.01	40.36 ± 14.17	3429.68 ± 166.01	4.83 ± 3.60	1,14,174.34 ± 41,553.65	1,24,340.64 ± 46,512.13

Table 6 – One-side F-test and T-test results of main parameters between F-I and F-II.

	AUC_{0-144} (ng h/ml)	$AUC_{0-\infty}$ (ng h/ml)	C_{max} (ng/ml)
F-test	$P > 0.05$	$P > 0.05$	$P < 0.05$
T-test	$P > 0.05$	$P > 0.05$	$P > 0.05$

As for matrix effect, all the ratios were between 85% and 115%, which means no matrix effect for AZI and ROX in this method.

3.3.5. *Stability*

The stock solution of AZI in plasma was found to be stable at sample room 7 °C for 6 h, at freeze and thaw stability (Table 4). The results from all stability tests presented demonstrated a good stability of AZI over all steps of the determination.

The validation above all met the demands of accurate quantification.

3.4. *Pharmacokinetic study*

Pharmacokinetic study of the two sustained-release tablets of AZI compared with commercial available dispersible tablet were investigated following oral administration of 500 mg in dogs. The mean concentration-time profiles for the three AZI tablets are shown in Fig. 4. The pharmacokinetic parameters for the three formulations are shown in Table 5. The mean peak plasma concentrations for F-I, F-II and AZI dispersible tablet were 4115.13, 3429.68 and 5558.55 ng/ml, and these were achieved at 3.17, 4.83 and 0.58 h, respectively. Compared with the reference, the C_{max} of F-I and F-II were decreased, and the T_{max} were prolonged, in that case which meet the requirements of sustained-release tablets. The relative bioavailability of F-I and F-II were 79.12% and 64.09%. Compared with the reference, the AUC_{0-144} of F-I and F-II decreased significantly.

T-test of AUC_{0-144}, $AUC_{0-\infty}$ and C_{max} for F-I and F-II were carried out (Table 6). We found there was no significant difference between F-I and F-II for AUC_{0-144}, and $AUC_{0-\infty}$, suggesting that the different release rate did not induce different pharmacokinetic in vivo. F-II which releases the drug slowly, allowed for a high dose to be administered, reduced gastrointestinal side-effects, increased the compliance of patients.

4. Conclusion

Two sustained-release AZI tablets (F-I and F-II) were prepared. The release rate of F-I and F-II were $T_{100\%} = 3$ h and $T_{100\%} = 8$ h in pH 6.0 phosphate buffer, respectively. However, the AUC_{0-144} and $AUC_{0-\infty}$ of F-I and F-II were no significantly different. F-II which releases the drug slowly, allowed for a high dose to be administered, reduced gastrointestinal side-effects, increased the compliance of patients, but did not change the pharmacokinetic behavior. Xanthan gum was a good skeleton material that made the release of AZI not affect by pH of dissolution medium. The relative bioavailability of F-I and F-II were 79.12% and 64.09% compared with the reference.

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